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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,918	06/27/2003	John B. Harley	OMRF:050USD2	6316

7590 06/01/2006

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EXAMINER	
LI, BAO Q	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/607,918	HARLEY ET AL.	
	Examiner	Art Unit	
	Bao Qun Li	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *6-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/27/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: sequence comply letter

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Please comply with the sequence rules for all the sequences disclosed in the current application or authorize to the sequence transfer for the divisional application 10,012,756 is there are not more new sequennces disclosed in the application.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

DETAILED ACTION

This is to acknowledge the preliminary amendment filed on June 27, 2003. Claims 8-9, 14, 21, 22-25 have been amended. Claims 1-26 are pending.

Election/Restrictions

Applicant's election without traverse of group I, claims 1-5 in the reply filed on March 24, 2006 is acknowledged. Therefore, claims 6-26 are withdrawn from consideration.

Informality Issues

The specification contains the following informality issues that are required to be corrected set forth bellow:

(1) ***Abstact***

The abstract of the disclosure is objected to because it contains more than 150 words. Normally, an abstract is limited to 150 words. Correction is required. See MPEP § 608.01(b).

(2) Sequence requirements

This application contains sequence disclosures **throughout the specification and claims** that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

For full compliance with the sequence rules, a complete response to this office action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with **both** these requirements in the time period set forth in this office action will be held non-responsive.

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility.

3. In the instant case, one of the scope of the claims are drawn to a composition comprising EBV virus or complete EBV proteins expressed by a recombinant DNA or RNA with sequence identical to the entire DNA or in RNA genome. Because the native EBV is a pathogen that causes either acute infection or latent infection (See attached article in webpage EBV-htm). It is well known in the art that EBV infection can cause both acute and latent infections in man. It is etiologic agent for several serious diseases and cancer developments, such as infectious mononucleosis, lymphoma, nasopharyngeal carcinoma and Hairy leukoplakia etc. Moreover, the EBV infection is also related to several autoimmune diseasess, such as rheumatoid arthritis, Sjogren's syndrome and systemic lupus Erythematosus (SLE) (See specification on pages 4-5). , Therefore, the composition comprising the entire native EBV virus lacks either a substantial asserted utility as well as any established utility.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. Moreover, claims 2 and 4 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing an immune response using an antigen peptide of EBV that are not derived from the peptides PPPGRRP, GRGRGRGG and RGRGREK, does not reasonably provide enablement for using said peptide for treating or preventing any autoimmune disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

7. The test of scope of enablement or enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art would render undue experimentation (See United States v. Theketronic Inc., 8USPQ2d 1217 (fed Cir. 1988). Whether undue experimentation is required is not based upon a single factor but rather a conclusion reached by weighting many factors. Theses factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in re Wands, 8USPQ2d 1400 (Fed. Cir. 1988) set forth bellow: (1). Nature of Invention, (2). Scope of the invention, (3). State of art, (4). Unpredictability in the field, (5). Number of working example, (6). Amount of guidance presented in the specification, and (7). Level of skill in the art.

8. The nature of the invention is based on the fact found by applicants that injection of EBV antigen epitope RGRGREK to produce a lupus like syndrome in a mouse model. Applicants then claim a composition for treating any or all autoimmune disease using EBV virus or any proteins or peptides derived from EBV. The scope of the claims reads on that composition comprising any or all EBV native virus, mutant virus, any or proteins or peptides encoded by the native EBD virus genome. The scope of claim 4 read on any protein or peptides sequences of EBV except the peptides PPPGRRP, GRGRGRGG and RGRGREK.

9. The state of art teaches that EBV infection cause many diseases and it may relate to some autoimmune diseases (EBV.htm). Because they found that the infection of EBV are more frequently found in EBV patients. James et al. reported that the EBV antigen epitope RGRGREK can induce mice having lupus syndrome and the EBV antigen epitopes PPPGRRP, GRGRGRGG and RGRGREK may cross-react with the SLE auto-antigen epitope PPPGMRPP (James et al. J. Clin. Inve. 1997, Vol. 100, No. 12, pp. 3019-3026, se Fig. 3). However, though EBV infection is

more common happened in autoimmune patients; not all autoimmune diseases are reported to have a high prevalence with EBV infection . The etiologies for all autoimmune disease are very complicated and even the etiology for of SLE is still very complicate. The fact is that not all SLE patients are EBV infected. There are many other factors also seem to play a role in SLE development as taught by Vaughan J. (J. Clin. Inves. 1997, Vol. 100, No. 12, pp. 2939-2940). The unpredictability is also disclosed by applicants in the specification. For example, applicants cite on page 26 of specification that rabbits immunized with map-PPPGMRPP seems to improve clinically after developing the most severe manifestations of systemic autoimmunity. However, on page 30, applicants also cites that Rabbits were immunized with PPGMRRP on a MAP™ backbone develop antibody beyond the immunized peptide and also usually develop autoantibodies ... and clinical features of SLE as well as other autoimmune syndromes as evidenced by James et al. (J. Exp. Med. 1995, Vol. 181, pp. 453-461). Applicants further disclose in the specification that mice immunized with peptide PPPGREK develop a lupus-like syndrome (page 31). Apparently, it is unpredictable for using the EBV virus or its deleted mutant or any components derived from ENV thereof, even if they are not the possible cross-antigens containing the peptide PPPGRRP, GRGRGRGG and RGRGREK to treat or prevent any or all autoimmune disease or even SLE. Up-to-date, there is no immunogenic composition comprising EBV antigenic component(s) found to be effectively for the treatment of EBV infection and its related autoimmune disorders, such as lupus, and no vaccine comprising EBV antigenic component(s) found to be able to prevent EBV infection. Accordingly, the level of developing such therapeutic agent or preventive medication is very difficulty and unpredictable (See Overview of the EBV by Vitacor laboratories on viracao.com; Systemic Lupus Erythematosus (SLE) Clinical Overview by Dr. Belmont on page 2, Vaughan J. (J. Clin. Inves. 1997, Vol. 100, No. 12, pp. 2939-2940)).

10. The current application only discloses that mice immunized with peptide PPPGREK develop a lupus-like syndrome. Applicants also teach in t the specification that the after EBV infection, development of antibodies against EBV antigen epitope of PPPGRRP bind to the autoimmune antigen epitopes, PPPGMRPP and PPPGIRGP appeared in SLE. They further teach a method for making a proper diagnostic and/or prognosis of systemic lupus erythematosus (SLE) caused by EBV via detecting a group of antibodies reactive to a group of antigen epitopes

identified by SEQ ID NO: 1-5 plus SEQ ID NO: 7, wherein the SEQ ID NO: 4-5 are positive markers of the SLE, the SEQ ID NOS 1-3 are EBV antigen epitopes, which are found to be cross-reactive auto-antigens with SLE epitope of SEQ ID NO: 4. The SEQ ID NO: 7 though is very frequently found in EBV infection, but it is not found bound with EBV infected SLE. Therefore, it is also important for serving as positive marker of EBV infection but negative marker for the prognosis of SLE development.

11. Beside the peptides PPPGRRP, GRGRGRGG and RGRGREK, Specification does not teach which one or more structures are related to any or all autoimmune disorders. The specification is completely deficient for teaching any in vitro or in vivo experiments of using any peptide derived from EBV to treat or prevent the EBV-induced autoimmune disorders.

12. Therefore, the specification does not provide sufficient evidence to support the claimed invention in claims 1, 3 and 5 as wee as the broad scope of the claims 2 and 4.

13. Hence, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1-3 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. Claims 1 and 3 are vague and indefinite in that the metes and bounds of "a component" are not defined. Moreover, claim 2 is vague and indefinite in that the metes and bounds of "one or more structures" are not defined. This affects the depended claim 5.

The following prior art rejections are made on the record that are based on the priority dates of claims as May 16, 1996 because the claimed inventions are not disclosed in the parental application No. 08/160,604

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Finerty et al. (J. Gen. Virol. 1992, Vol. 73, p. 449-453) or Morgan et al. (A) or (B) (J. Medical Virol. 1989, Vol. 29, pp. 74-78), (Vaccine 1992, Vol. 10, pp. 563-571).

19. Finerty et al. or Morgan et al. in both (A) and (B) teach an immunogenic composition comprising a recombinant envelope glycoprotein gp340 of EBV with alumni adjuvant (Finerty et al.) or a synthetic muramyl dipeptide adjuvant emulsified in squalane containing a pluronic polymer (Morgan et al. A at pages 74-75 or B at page 5640), wherein the envelope protein is expressed as a recombinant protein encoded by the EBV envelope glycoprotein rather than the entire genome of EBV or the component that can induce an autoimmune disorder.

20. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Milman et al. (Proc. Natl. Sci. USA, 1986 Vol. 82, pp. 6300-6304).

21. Milman et al. disclose a composition comprising a recombinant EBV nuclear protein 1, said recombinant protein is encoded by only partial sequence of EBV nuclear protein 1 gene in that its N-terminal and C-terminal are all partially deleted (See Fig. 1). The 28-kDa recombinant protein is purified with linear gradient of 0-250 mM sodium phosphate (pH 7.5) in 250 mM NaCi/50 mM Tris Cl, pH 7.5. The purified EBNV suspended in Freund's's complete adjuvant was administered into rabbits for inducing an antibody against the EBV nuclear antigen-1 (See page 6301). Said antigen polypeptide is also immunoreactive to the human sera collected from the patients infected with EBV (See Fig. 5).

22. Claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Ambinder et al. (J. Virol. 1991, Vol. 65, No. 3, pp. 1466-1478).

23. Ambinder et al. teach a recombinant vector or plasmid DNA comprising the sequence encoding several truncated EBV nuclear antigen –1 polypeptide fragments. They also teach to use said plasmids to transfect host cells for expressing the recombinant EBV nuclear antigen truncated forms in the solution containing BES-buffered modified saline (See pages 1468). Therefore, the claimed invention is anticipated by the cited reference.

24. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by US patent No. 4,707,358

25. US patent "358" disclose an immunogenic composition comprising an immunogenic peptide and a pharmaceutical carrier, wherein said peptide antigen is surface antigen of EBV and expressed as a recombinant protein (See entire document, especially claims 1-2). Therefore, the claimed invention is anticipated by the cited reference.

26.

27. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Rhodes et al. (I Immunol. 1985, Vol. 134, No. 1, pp. 211-216)

28. Rhodes et al. teach an immunogenic composition comprising synthetic peptide conjugated with keyhole limpet hemocyanin and either Freund's complete adjuvant or Freudent's incomplete adjuvant (See page 211), wherein the peptide is derived from the EBV nuclear antigen-1 that does not contain any of the sequences listed in claim 4 (See Table II on page 214). Therefore, the claimed invention is anticipated by the cited reference.

Claim Rejections - 35 USC § 102

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

30. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Finerty et al. (Vaccine 1994, vol. 12, No. 13, pp. 1180-1184) or Gu et al. (Dev. Biol. Stand. 1995, Vol. 84, pp. 171-177)

31. Finerty et al. teach an immunogenic composition comprising a recombinant envelope glycoprotein gp340 of EBV and an alumni adjuvant, wherein the envelope protein is expressed as a recombinant protein encoded by the EBV envelope glycoprotein rather than the entire genome of EBV or the component that can induce an autoimmune disorder.

32. Claims 1-2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Gu et al. (Dev. Biol. Stand. 1995, Vol. 84, pp. 171-177)

33. Gu et al. teach an immunogenic composition comprising a recombinant vaccinia virus encoding the envelope glycoprotein gp340 of EBV with a synthetic muramyl dipeptide adjuvant formulation or ISCOM (Gu et al. page 572), wherein the envelope protein is expressed as a recombinant protein encoded by the EBV envelope glycoprotein rather than the entire genome of EBV or the component that can induce an autoimmune disorder.

34. For the above rejections, Applicants are reminded that regarding to the limitations of "for alleviating or preventing autoimmune disorders" cited in claims 1-2 and 5, and "for administration of the virus or virus component ---" cited in lines 4-5 of claim 1, they are considered as preamble languages and product by process, because they do not add any patentable weight in term of the distinctness of the structure characteristics of the claimed product. To this context, the claimed product is anticipated by the cited reference.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 571-272-0904. The examiner can normally be reached on 6:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bao Qun Li
05/23/2006

BAOQUN LI, MD
PATENT EXAMINER